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ARNOLD & PORTER LLP
ATTN: IP DOCKETING DEPT.
555 TWELFTH STREET, N.W.
WASHINGTON, DC 20004-1206

| EXAMINER | |
|---|---|
| HUMPHREY, LOUISE WANG ZHIYING | |
| **ART UNIT** | **PAPER NUMBER** |
| 1648 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 03/22/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/740,694 | ARIMILLI ET AL. | |
| | Examiner | Art Unit | |
| | Louise Humphrey, Ph.D. | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,30-33,62-65,93-96 and 123-125* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,30-33,62-65,93-96 and 123-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This Office Action is in response to the amendment filed 20 December 2006. Claims 4-29, 34-61, 66-92, 97-122, and 126-180 have been cancelled. Claims 1-3, 30-33, 62-65, 93-96, and 123-125 are pending.

### *Response to Arguments*

Claim Rejections - 35 U.S.C. §112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 2, 3, 30-33, 62-65, 93-96, and 123-125 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is **withdrawn** in view of Applicants demonstration of possession of claimed invention by pointing to the specification, *i.e.* page 1690, lines 7-8, and pages 1691-1694, that supports the limitation of an extract of peripheral blood mononuclear cells.

The rejection of claim 1 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is **maintained**.

Examiner's rejection in the Action mailed on 7 September 2006 is as follows:

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the

claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." M.P.E.P. §2163.

In the instant case, the claims are directed to a method for identifying a candidate compound as a suitable pro-drug using an extract of peripheral blood mononuclear cells (PBMC) having carboxylic ester hydrolase activity to convert a candidate compound into a metabolite compound or using GS-7340 Ester Hydrolase. The claims are drawn to genus of carboxylic ester hydrolases that are only defined by molecular weight range and the isoelectric point.

The only factor present in the specification is the physical and/or chemical properties: a molecular weight around 70-100 kDa, and a pI around pH 4.5-5.5 (p.1694-1698). The specification provides description for a single method of isolation, which yields an extract comprising ester hydrolysis activity. However, Applicants have not purified the enzyme to homogeneity and performed amino acid analysis to elucidate the structure of the instantly claimed products. There is no identification of any partial structure that correlates with the ester hydrolysis function.

As discussed above, the skilled artisan cannot envision the detailed chemical structure and function of the claimed GS-7340 Ester Hydrolase or the genus of carboxylic ester hydrolases. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of cloning or isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. A definition by function alone "does not suffice, to sufficiently describe a coding sequence" because it is only an indication of what the gene does, rather than what it is." *Eli Lilly*, 119F.3 at 1568, 43USPQ2d at 1406.

The genus of carboxylic ester hydrolases contains about 79 different enzymes (www.brenda.uni-koeln.de/ectree/index.php4?ID=75&stype=7&PHPSESSID= c7af8a6f051020fcb37ac30a2aba5fc6 ). The single method of isolation of PBMC extract does not reflect the variance in this genus because the specification does not identify the characterized vs. the uncharacterized and the known vs. the unknown carboxylic ester hydrolases in the claimed PBMC extract. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483, claims directed to mammalian FGF's were found to be unpatentable due to lack of written descriptions for that broad class. Accordingly, it is deemed that the specification fails to provide adequate written description for the claims and does not reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants argue that the specification discloses a PBMC enzyme which is designated as GS-7340 Ester Hydrolase, the protocol for the method of extraction of GS-7340 Ester Hydrolase, chromatography, and an actual purification summary.

Applicants' arguments have been fully considered but are not persuasive to overcome the rejection of the genus of an extract in claim 1. The issue raised in this rejection is whether or not applicants were in possession of a reasonable number of sources of hydrolase activity to support the full breadth of the claim language directed toward enzyme activity obtained by *any* extract. The limitation "an extract" does not limit the claim to any particular tissue or cell type. The genus of an extract encompasses extracts from a variety of cell types and tissue sources including all kinds of epithelial cells, hepatocytes, hormone secreting cells, barrier function cells (lung, gut, exocrine glands and urogenital tract), extracellular matrix secretion cells, contractile cells, blood and immune system cells, sensory transducer cells, autonomic neuron cells, central nervous system neurons and glial cells, pigment cells, germ cells. Claim 1 is also drawn to any unknown and uncharacterized carboxylic ester hydrolase from an extract.

The only cell type described in the prior art for the extraction of carboxylic ester hydrolase is associated with the hematopoietic compartment in a human body. For example, Lam *et al.* describe carboxylic ester hydrolase activity in human monocytes (1978) and Lee *et al.* describe human esterase D in human erythrocytes (1986). The specification only discloses one embodiment in an extract of PBMC, which does not allow one skilled in the art to reasonably envision the chemical structure of the claimed genus of an extract that correlates with carboxylic ester hydrolase activity. Since it is unpredictable in the art whether the other claimed cell type or tissue source can meet the requisite limitations in the claim, the only working embodiment provided by the

Applicants does not represent the entire genus of extract. Therefore, Applicants are not in possession of *any* extract capable of catalyzing the hydrolysis of a carboxylic ester.

## Claim Rejections - 35 U.S.C. §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 1-3 under 35 U.S.C. §102(b) as being anticipated by Eisenberg *et al.* (2001, NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, Vol. 20, Issue No.4-7) is **withdrawn** in view of Applicants argument that the cited reference, with issue numbers corresponding to April through July, is not published more than one year before the effective filing date of 26 April 2002. The authors of this reference are the same as the inventors of this application.

## New Claim Rejections

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 30-33, 62-65, 93-95, and 123-125 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, the phrase "capable of" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention.

Claim 2 is rejected for depending from claim 1.

Claims 30-33, 62-65, 93-95, and 123-125 recite "GS-7340 Ester Hydrolase," which is unclear whether the claims drawn to one specific carboxylic ester hydrolase enzyme or a partially purified fraction of a peripheral blood mononuclear cell (PBMC) extract, comprising GS-7340 Ester Hydrolase enzymes with a range of molecular weight and the range of isoelectric point. The phrase "GS-7340 Ester Hydrolase" implies an enzyme purified to homogeneity, however, the specification neither defines the amino acid sequence or any other structural information of the claimed GS-7340 Ester Hydrolase, nor discloses whether the final product of the purification process is purified to homogeneity or contains contaminant proteins. This rejection can be obviated by amending the claims to recite "a partially purified fraction of a PBMC extract comprising GS-7340 Ester Hydrolase activity."

Claim 1 rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method comprising contacting a candidate compound with a *PBMC extract* having carboxylic ester hydrolase activity, does not reasonably provide enablement for a method comprising contacting a candidate compound with *any other extract* having carboxylic ester hydrolase activity. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make the invention commensurate in scope with these claims.

Enablement is considered in view of the *Wands* factors (MPEP §2164.01(a)). In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986).

The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The nature of the invention is a method for identifying a candidate compound as a suitable pro-drug comprising contacting a candidate compound having an esterified phosphonate group or an esterified carboxyl group, with an extract capable of catalyzing the hydrolysis of a carboxylic ester to produce a metabolite compound. The breadth of the claims encompass extracts from a variety of cell types and tissue sources including all kinds of epithelial cells, hepatocytes, hormone secreting cells, barrier function cells (lung, gut, exocrine glands and urogenital tract), extracellular matrix secretion cells, contractile cells, blood and immune system cells, sensory transducer cells, autonomic neuron cells, central nervous system neurons and glial cells, pigment cells, germ cells.

Claim 1 is also drawn to any unknown and uncharacterized carboxylic ester hydrolase from an extract.

The state of the prior art suggests that extracts, obtained from human cells with hematopoietic origins, are capable of catalyzing the hydrolysis of a carboxylic ester to produce a metabolite compound, as evidenced by Lam *et al.*, who teach an aryl acetic ester hydrolase isolated from human monocytes (1978), and Lee *et al.*, who teach isolation of human esterase D in human erythrocytes (1986). The specification only discloses one working example, an extract of PBMC, which does not support the full breadth of the claims. There is no direction or guidance on how to isolate or purify and use any other type of extract to catalyze the hydrolysis of a carboxylic ester in the candidate compound and produce the metabolite compound. Therefore, the amount of guidance does not correlate with the claimed method.

Given the limited guidance in the specification and teaching in the art, one skilled in the art would be burdened with undue and unpredictable experimentation to identify all extracts comprising carboxylic ester hydrolase by trial and error. Absent working examples and specific teaching in the art regarding all cell type extracts comprising ester hydrolases, those in the art would not be able to use the claimed method.

***Allowable Subject Matter***

Claims 3, 30-33, 62-65, 93-96, 123-125 would be allowable if rewritten or amended to overcome the rejections under 35 U.S.C. §112, 2nd paragraph, set forth in this Office action.

Claim 2 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. §112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter: claims 2, 3, 30-33, 62-65, 93-96, and 123-125 are free of prior art of record. The Examiner is not aware of any suggestion in the prior art of record that would point the artisan to the claimed method of identifying a pro-drug comprising (1) hydrolyzing the carboxylic ester of a candidate compound with a partially purified extract of PBMC comprising GS-7340 Ester Hydrolase to produce a metabolite compound; and (2) determine if the metabolite compound has a phosphonic acid group instead of the esterified phosphonate group of the candidate compound, or carboxylic acid group instead of the esterified carboxyl group of the candidate compound.

***Contact Information***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
16 March 2007

Louise Humphrey, Ph.D.
Assistant Examiner